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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,485	06/17/2005	Michael Barry Gravestock	100858-1P US	2450

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ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding..

Office Action Summary	Application No.	Applicant(s)	
	10/539,485	GRAVESTOCK ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 1-11, 14 and 15 in the reply filed on 6/9/2006 is acknowledged. Claims 1-11, 14 and 15 will be examined to the extent they embrace the elected subject matter. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants' amendment to claims 2-11 is also acknowledged.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 8/10/2005, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of "in vivo hydrolysable ester" in claims 1, 9 and 15 is deemed as indefinite as esters or carbamates in general and as noted in specification, are compounds, which undergo in vivo hydrolysis In that sense recitation of "in vivo hydrolysable esters" is not ambiguous and is acceptable. However, the definition of various substituent groups on C and R_1b include such groups, namely esters, carbamates, alkoxycarbonyl etc. which are also in vivo hydrolysable and therefore it is not clear what is the difference between these variable groups and the "in vivo hydrolysable ester" groups.

   The use of ester group(s), carbamates etc as substituents on C and R_1b and In vivo hydrolysable ester as Markush choice, results in ambiguity.

   Claims 10 and 15 recite prodrug. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable groups include such groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

2. Recitation of " R_1a" in claim 9 renders claim 9 indefinite, as there is no R_1a label in claim 9. Claim 9 has R_2b which lacks a definition. In addition, claim 9 will become a duplicate when non-elected subject matter is removed form claim 1 leading to a double patenting rejection.

3. Claim 10 and 15 are improper dependent claims as they recite prodrug which is not recited in claim 1 on which claims 10 and 15 are dependent.

4. Regarding claim 15, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

5. The process embraced in claim 15 is also indefinite for more than one reason. In general, the process claim is vague and clear due usage of loose terms. For example, the terms hydrogenated version, replaceable substituents, complimentary pairs of substituents suitable as complementary substrates,

desired cross coupling etc., are unclear and not precise enough delineate what process is being claimed. In addition, process a is cryptic and does not precisely state what process is being claimed. The same is true for "leaving group useful in palladium coupling". It appears that one has to find out what these leaving groups are and then redeem such groups as part of instant invention without the claim actually reciting them.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making in-vivo hydrolysable of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug , in this case in vivo hydrolysable ester is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and

produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in the passage spanning pages 18-19 c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. I) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making

Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating both Staphylococcus aureus and Streptococcus pneumoniae, does not reasonably provide enablement for treating any or all Gram-positive and Gram- negative bacterial infections generically embraced in the instant invention. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant method of use claim 11 is drawn to a "method for producing antibacterial effect in a warm blooded animal". Instant claim 11, as recited, is a reach through claim. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of growth of selected bacteria by the instant compounds, claim 11 reaches through treating any or all bacterial infections, in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of Staphylococcus aureus and Streptococcus pneumoniae bacteria, based on limited assay with limited bacteria, it is claimed that treating any or all bacterial infections in general for which there is no enabling disclosure. Method claim 11 is not adequately enabled for treating any or all Gram-positive and Gram- negative bacterial infections generically embraced in the instant invention. From the reading of specification, it appears that the applicants are asserting that the embraced compounds because of their mode action as inhibitors of some bacteria, would be useful for treating any or all Gram-positive and Gram- negative bacterial infections, for which, there is no supporting disclosure in the specification. For example, as recited, the list of bacterial

infection would include gram-positive bacteria, including cocci such as Staphylococcus species and Staphylococcus species, acid-fast bacterium, including Mycobacterium species, bacilli, including Bacillus species, Corynebactedum species and Clostridium species, filamentous bacteria, including Actinomyces species and Streptomyces species', gram-negative bacteria, including cocci such as Neisseria species and Acinetobacter species, bacilli, such as Pseudomonas species, Brucella species, Agrobacterium species, Bordetella species, Escherichia species, Shigella species, Yersinia species, Salmonella species, Klebsiella species, Enterobacter species, Haemophilus species, Pasteurella species, and Streptobacillus species, spirochetal species, Campy/obacter species, Vibrio species, and intracellular bacteria including Rickettsiae species and Chlamydia species. Specific bacterial species that are targets for the antibiotics of the invention include Staphylococcus aureus Staphylococcus epidermidis, Staphylococcus saprophyticus, Stœptococcus pyogenes; Streptococcus agalactiae, Stœptococcus pneumoniae, Enterococcus faecalis, Enterococcus faecium Bacillus anthracis, Mycobacterium avium, Mycobacterium tuberculosis, Acinetobacter baumannii; Corynebacterium diphtheria, Clostddium perfringens, Clostridium botulinum, Clostridium tetani, Neisseria gonorrhoeae, Neisseria meningitidis, Pseudomonas aeruginosa, Legionella pneumophila, Escherichia coli, Yersinia pestis, Haemophilus influenzae, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Vibrio cholerae, Vibrio parahemolyticus, Trepomena pallidum, Actinomyces israelli, Rickettsia prowazekii, Rickettsia rickettsii, Chlamydia trachomatis, Chlamydia psittaci, Brucella abortus, Agrobacterium tumefaciens; and Francisella tularensis, for which there is no

adequate written description and enabling disclosure.

However, there is no competent evidence in the specification that such an inhibition in the assay conditions would result in the effective treatment of any or all bacterial infections. Moreover many if not most, bacterial infections such as meningitis, anthrax etc. are very difficult to treat and at present there is no known drug, which can successfully be used to treat infectious diseases. Despite the fact there are several commercial antibacterial agents are available, it is still difficult to treat several pathogens such as those cause leprosy, meningitis, sexually transmitted infections, anthrax etc.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288 . Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. For bacterial infection, see Snyder et al., J. Med. Liban 48(4): 208-214, 2000 (PubMed Abstract provided), wherein with regards to antibacterial therapies, it is stated that " common bacteria whose susceptibility to antimicrobials is no longer predictable". Note also that despite the fact there are several

commercial antibacterial agents are available, it is still difficult to treat several pathogens such as those cause leprosy, meningitis, sexually transmitted infections, anthrax etc.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating any or all bacterial infections that require inhibiting activity of instant compound.

2) The state of the prior art: Although there are large number antibacterial agents, none of them are claimed or shown to be useful in treating any or all bacterial infections.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for treating any or all bacterial infections. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples for treating any or all

bacterial infections and the state of the art is that the effects of bacterial agents based on the disclosed inhibitory activity are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all bacterial infections as well as millions of compounds.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating variety of bacterial infections of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro activity of compounds shown in examples of species, does not reasonably provide enablement for large genus of compounds generically embraced in the definition of C ring and R_1b. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Representative examples of structurally diverse compounds generically embraced in the invention are not shown to possess in vitro activity much less in vivo uses claimed herein. Instant genus of oxazolidinone bearing pyridine-phenyl core, embrace compounds with substituents bearing plethora of structural cores and functional groups and other groups permitted at instant C and R_1b variables which include variously substituted heterocyclic rings with variable ring sizes and variable heteroatoms variety of reactive functional groups such COOH, OH ,SH, amido, sulfoxides, sulfones nitrile, carbamates, etc. The genus embrace millions of compounds and specifcation has one example of the genus. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same bioactivity profile since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive art such as the pharmaceuticals.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method of use. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

8/17/2006